REMARKS

Claims 1, 2, 4, 16, 18, 21 and 22 are currently under examination. Claim 22 is amended herein to identify an amino acid sequence by the proper sequence identifier. Claim 40 is added herein. Support for new claim 40 can be found in the claims as filed, on page 43, lines 5-7 and elsewhere throughout the specification. No new matter is believed to be added by these amendments. Therefore, pursuant to the following remarks, Applicants respectfully request entry of these amendments and allowance of the claims to issue.

Objection to the Specification

The Office Action states that the specification is objected to as allegedly failing to provide proper antecedent basis for claimed subject matter. The Examiner has acknowledged that claim 38 provides support for the term "adenoviral signal sequence" and has suggested that the phrase be introduced into the specification on page 23, before the mention of the adenoviral E19 signal sequence.

As suggested by the Examiner, the first paragraph on page 23 is amended herein to provide proper antecedent basis for the term "adenoviral signal sequence." Therefore, Applicants believe this objection has been overcome and respectfully request its withdrawal.

Sequence Rules

The Office Action alleges that pages 23, 40, 41 and 44 of the specification and claim 22 contain sequences not identified by a SEQ ID number. Furthermore, the Office Action states that the nucleic acid sequence on page 44, line 10, is allegedly not found within the submitted sequence listing.

In response, the specification is amended herein to identify the sequences set forth on pages 23, 40, 41 and 44 with a SEQ ID number. The Sequence Listing has also been amended to include all of the sequences set forth on page 44. Enclosed herewith is a diskette containing a substitute Sequence Listing for this application in computer readable form (CRF) and a paper copy of the substitute Sequence Listing in compliance with 37 C.F.R. § 1.821-1.825. Applicants

hereby certify that the information in the computer readable form on the diskette and in the hard copy of the Sequence Listing is the same and includes no new matter. The enclosed computer readable copy and paper copy of the Sequence Listing are believed to bring the Sequence Listing into full compliance with the sequence rules. Therefore, Applicants believe that the objections regarding the sequences set forth in the Application have been overcome. Thus, Applicants respectfully request their withdrawal.

Rejection Under 35 U.S.C. § 102(b)

The Office Action states that claims 1, 2, 18, 21 and 22 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Restifo et al. (U.S. Patent No. 5,733,548, March 1998) as evidenced by Tandle et al. (J. Trans. Med., 2004). According to the Office Action, vaccinia particles bearing a sequence encoding the E19/P1A fusion protein could induce an immune response which lysed P815 tumor cells, and thus, according to the Examiner, the E19/P1A fusion is considered to be an antiangiogenic protein. The Examiner has obtained guidance on the interpretation of "antiangiogenic protein" from Tandle et al. (*J. Trans. Med.*, 2004), Figure 1, which indicates that angiogenic inhibitors, in the context of antiangiogenic gene therapy, include direct and indirect inhibitors. Included in the indirect inhibitors are inhibitors of tumor cells, which prevent the expression of angiogenic growth factors and receptors. Thus, according to the Office Action, Restifo et al., by lysing p815 tumor cells (or any other tumor cell) using the E19/P1A fusion protein, inhibit tumor cells. The Office Action concludes that this inhibition indirectly inhibits angiogenesis, and therefore the E19/P1A protein is considered by the Examiner to be an antiangiogenic protein.

Applicants respectfully point out that Restifo et al. utilized small peptides fused to a signal sequence, for example, E19/P1A, as an immunogen to elicit a T cell response. These activated T cells were reactive against a tumor peptide and caused tumor cell lysis. Thus, it is the activated T cell that causes tumor cell lysis and not the E19/P1A fusion protein. One of skill in the art would readily recognize that the fusion proteins of Restifo et al. have no other activity than to act as immunogens and would not be considered antiangiogenic proteins. Although the Examiner has utilized Tandle et al. to obtain guidance for the term "antiangiogenic protein,"

Applicants respectfully point out that none of the direct antiangiogenic inhibitors or indirect antiangiogenic inhibitors set forth in Tandle et al. inhibit angiogenesis via T cell activation by a peptide immunogen. Therefore, none of the activities for the direct or indirect angiogenesis inhibitors set forth by Tandle et al. are analogous to the activity of the E19/P1A fusion protein of Restifo et al. which acts as an immunogen to stimulate a T cell response to a tumor peptide. Applicants respectfully remind the Examiner that extrinsic evidence may be used to explain but not expand the meaning of terms and phrases used in the reference relied upon as anticipatory of the claimed subject matter. In re Baxter Travenol Labs., 952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991). Since Tandle et al. does not describe immunogenic T cell activation as a mechanism for antiangiogenesis the Examiner cannot rely on Tandle et al. to define the E19/P1A fusion protein of Restifo et al. as an antiangiogenic protein. For the reasons set forth above, Applicants assert that the E19/P1A fusion protein of Restifo et al. is not an antiangiogenic protein. Therefore, Restifo et al. does not disclose a compound comprising a recombinant nucleic acid encoding an antiangiogenic protein operatively linked to an adenovirus signal sequence inserted within a viral nucleic acid. Thus, Applicants respectfully request withdrawal of this rejection as it applies to claims 1, 2, 18, 21, 22. For the reasons set forth above, this rejection should not apply to new claim 40.

Rejection Under 35 U.S.C. § 103(a)

The Office Action states that claims 1, 2, 4, 16, 18, 21 and 22 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Li et al. (US Patent No. 6,638,502) in view of Restifo et al.

According to the Office Action, the claimed recombinant nucleic acids are allegedly disclosed by both Li et al. and Restifo et al. with the exception of endostatin (Restifo) and the E19 signal sequence (Li). Further stated in the Office Action is that the ordinary skilled artisan, seeking a composition to treat cancer, would have allegedly been motivated to use endostatin with the compositions taught by Restifo et al. because Li et al. teaches endostatin to be a well known and desirable type of antiangiogenic protein having utility for preventing tumor growth. The Office Action also states that the same artisan would have allegedly been motivated to use

the E19 signal sequence of Restifo et al. with the adenoviral vectors of Li et al. because Restifo teaches the E19 sequence to be a well-known and functional secretion signal, and Li et al. teaches the interchangeability of different signal sequences to secrete the desired antiangiogenic protein.

Applicants respectfully point out that there is no motivation to combine Restifo et al. (US Patent No. 5,733,548) with Li et al. (U.S. Patent No. 6,638,502) because Restifo et al. discloses administration of a P1A tumor peptide (SEQ ID NO: 6 (9 amino acids)) linked to an adenoviral E19 signal sequence in order to induce an immune response and Li et al. discloses intratumoral administration of an adenoviral vector that expresses endostatin (185 amino acids). It is clear that the P1A tumor peptide of Restifo et al. is both structurally and functionally different from the much larger full-length endostatin, disclosed by Li et al. Therefore, Restifo et al. is nonanalogous art and would not be combined with Li et al. Furthermore, since there is no indication in either reference that the delivery system of Restifo et al. could deliver a much larger antiangiogenic protein, such as endostatin, there is no motivation to combine Restifo et al. with Li et al.

Even if one of skill in the art were motivated to combine Restifo et al., with Li et al., and they were not, there would be no expectation of success that delivering a viral vector comprising a nucleic acid encoding an antiangiogenic protein, for example, endostatin, linked to an adenovirus E19 signal sequence would result in sufficient expression of the antiangiogenic protein to achieve antiangiogenic activity via systemic administration. Applicants point out that operatively linking the adenovirus E19 signal sequence to the antiangiogenic protein imparted the unexpected property of increasing circulating levels of the antiangiogenic protein. This unexpected property resulted in a composition that has the ability to treat tumors via systemic delivery. None of the compositions disclosed in the prior art have this property nor does the prior art suggest how to impart this property. Prior to Applicants' invention, there was no evidence that any composition would result in increased expression of an antiangiogenic protein, much less result in sufficient expression of an antiangiogenic protein to overcome the failures associated with systemic delivery. Thus, the present invention provided a significant breakthrough in anti-tumor therapy. For the reasons set forth above, Applicants believe that

claims 1, 2, 4, 16, 18, 21 and 22 are unobvious over Li et al. in view of Restifo et al. For the same reasons, this rejection should not apply to new claim 40. Thus, Applicants respectfully request withdrawal of this rejection.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $1,220.00 is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Lizette M. Fernandez
Registration No. 46,694

NEEDLE & ROSENBERG, P.C.
Customer Number 36339
(678) 420-9300
(678) 420-9301 (fax)

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